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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
17VV-137270

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Application Number	Filed
09/927,914	August 10, 2001

First Named Inventor
Timothy P. Tully

Art Unit	Examiner
1627	Yong Soo Chong

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 33754.

☐ attorney or agent acting under 37 CFR 1.34.
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/djpelto Reg. No. 33754/
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Don J. Pelto
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202-218-0000
Telephone number

August 27, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	09/927,914	Confirmation No. 5180
Applicants	Timothy P. Tully	
Filed	10 August 2001	
TC/Art Unit	1627	
Examiner	Yong Soo Chong	
Docket No.	21RE-137270	
Customer No.	68850	

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Applicant respectfully requests review of the final rejection in the above-identified application. This Pre-Appeal Brief Request for Review is being filed concurrently with a Notice of Appeal and is submitted for the reasons stated on the attached sheets.

ARGUMENTS

Claims 1, 4-8, 100-104,[1] and 107-108 are pending in the application. Claims 3, 11, 14-20, 23, 49-58, 60-64, 94-99, and 105-106 have been cancelled, and claims 2, 9-10, 12-13, 21-22, 24-48, 59, and 65-93 have been withdrawn by the Examiner as being drawn to a non-elected invention. Favorable reconsideration of this application is respectfully solicited in view of the following arguments.

I. The Combination of Cited References Fails to Teach or Suggest All Claim Limitations.

Claims 1, 4-8, 100-104, and 107-108 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent 5,547,979 ("Christensen") in view of the Merck Manual ("Merck"). Final Office Action, mailed April 27, 2010 ("OA"), page 4. A *prima facie* case of obviousness requires that the cited references teach or suggest all the claim elements.[2] Here the pending claims all include the elements of administering a PDE4 inhibitor in conjunction with cognitive training and also repeating this administering

[1] The Applicant cancelled claims 100-1004 in the Reply mailed June 28, 2010 ("June Reply"), but the Amendment was not entered.

[2] *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *See, also CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) ("[O]bviousness requires a suggestion of all limitations in a claim.")

step one or more times. Administering "in conjunction" is not merely combining PDE4 inhibitor administration and cognitive training; it requires combining the two treatments such that CREB pathway function is enhanced in the appropriate neurons *during* training. *See* Applicant's Reply, mailed June 28, 2010 ("June Reply"), page 13. The obviousness rejection is insufficient, because it fails to teach or suggest these elements of the claims. *See* June Reply, pages 14-18. This failure reflects the Examiner's reliance on at least two faulty premises, the major errors and deficiencies of which are summarized as follows:

A. The Examiner errs by relying on a misplaced, incomplete, and erroneous view of Christensen.

As an alleged basis for administering a PDE4 inhibitor during stroke rehabilitation, the Examiner improperly asserts Christensen as teaching claim elements that it simply does not – and cannot – teach. According to the Examiner, Christensen "*clearly* teaches, in general, the treatment of a stroke *patient*, by administering a PDE4 inhibitor, which *encompasses the entire treatment regiment including rehabilitation.*" OA, page 9 (emphasis added).

The Applicant has repeatedly pointed out the multiple flaws in this argument. *See* June Reply, pages 14-16. First, it is misplaced, relying entirely on claim 1 of Christensen – reproduced here – which does not even recite treating a stroke *patient*, much less treating a stroke patient *during rehabilitation*:

> 1. A method of treating tissue injury, reperfusion injury, myocardial infarction, stroke or circulatory shock in a mammal, which comprises administering to said animal in need thereof an effective TNF inhibiting amount of a compound according to the formula . . ..

Instead, claim 1 of Christensen is directed to using a TNF inhibitor to treat acute medical *conditions* (including stroke) that are triggered or exacerbated by TNF – a cytokine produced during the *initial* stages of an inflammatory event. This misplaced reliance on claim 1 is further flawed because it fails to consider Christensen as a whole: The Examiner ignores all other disclosures in Christensen that bear on TNF action and stroke, disclosures that uniformly corroborate an acute and narrow therapeutic window for PDE4 inhibitor administration, as set forth in claim 1 of Christensen. *See* June Reply, pages 14-16.

Second, the Examiner argues that "it is not clear when exactly does inflammation subside during the treatment period of a stroke patient, since low levels of inflammation could last well into the rehabilitation period." OA, page 8. This argument is wrong because it relies on another incorrect presumption based on Christensen: that one skilled in the art would administer a PDE4 inhibitor beyond the acute stage of stroke. As just noted, this presumption is directly contradicted by Christensen itself. It is also contradicted by the prior art as a whole. For example, the Applicant has previously submitted a wealth of references that not only confirm a narrow therapeutic window for TNF inhibitor administration, but that also counsel *against* administering PDE4 inhibitors beyond the acute inflammatory stage of stroke.

See Applicants' Supplemental Response, mailed August 7, 2009 ("Supplemental Response"), pages 15-19.

Third, in connection with this assertion, the Examiner "reminds the Applicant that "the standard for obviousness is not absolute but a reasonable expectation of success." OA, page 8. But a "reasonable expectation of success" relates to the ultimate conclusion of obviousness; it does not apply to the threshold inquiry of what the prior art teaches in the first place. The Examiner still fails to identify any proper teaching – express or inherent – to administer a PDE4 inhibitor beyond the acute inflammatory phase. Nor has the Examiner identified any basis in the prior art for administering PDE4 inhibitors in *conjunction* with cognitive training, much less *repeating* this step one or more times – as the claims require.

Despite this evidence, the Examiner maintains an improperly broad view of Christensen in the Advisory Action, mailed July 16, 2010 ("Advisory Action"), page 2, asserting that "[o]ne of ordinary skill in the art would interpret the teachings of Christensen to administer the PDE4 inhibitor after the acute phase of stroke episode since a full clinical diagnosis must be made before any treatment regimen is to be implemented." Again, the Examiner provides no specific basis for this assertion, which, yet again, contradicts the evidence of record. Notably, this assertion contradicts the explicit statement in Merck that "[t]o be effective, treatments to minimize brain damage from acute stroke have to begin very soon after stroke onset." *See* June Reply, page 16.

In sum, it is respectfully asserted that the Examiner's view of Christensen finds no proper support in the prior art and, in fact, contradicts the teachings of the prior art. There is no adequate showing – nor is one possible – that the prior art teaches or suggests all elements of the claimed invention. On this basis alone, the Examiner's *prima facie* case is deficient, failing to include "articulated reasoning with some rational underpinning to support the legal conclusion."[3]

B. The Examiner errs by failing to consider pending claims of record and relying on a deficient and erroneous view of Merck.

The Examiner continues to ignore the plain language of the claims and maintains the argument that "Applicant's assertion that Christensen is simply teaching the administration of rolipram during the acute phase of stroke to reduce TNF *still* meets the limitations of the instant claims as it relates to the Merck Manual Reference." OA, page 10. The Applicant has made clear on the record that this argument does not apply to pending claims that restrict PDE4 inhibitor administration and cognitive training to the rehabilitation phase. June Reply, page 17. However, the Examiner dismissed this argument in the Advisory Action, asserting that it "assum[es] that the claim amendments have been entered into the record, which it has not since prosecution is now closed." Advisory Action, page 2. The Examiner is incorrect: claim 1, for example, was amended in January 2010 to include these limitations and hence *is* of record. *See*

[3] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Applicant's Reply, mailed January 28, 2010, page 2. The Advisory Action is therefore incomplete.

Moreover, Applicant submits that the Examiner's arguments are based on the misguided assessment that Merck teaches or suggests that the acute phase of stroke overlaps with cognitive protocols during rehabilitation. *See* June Reply, page 17. Specifically, the Examiner fails to acknowledge and address the explicit division of "stroke care" in Merck into two temporally distinct phases: "Immediate Care" and "Rehabilitation and Aftercare" *Id.* In this regard, the Examiner also fails to acknowledge or recognize that "Immediate Care" only includes "passive exercises" and does not mention or suggest cognitive training protocols (which are active procedures). *Id.* Hence, a correct and proper reading of Merck directly contradicts the Examiner's assertion that Merck "clearly states that a training protocol should be started as early as possible towards a patient's rehabilitation to stroke." *Id.*

Despite the consistent evidence to the contrary, the Examiner continues to confound the teachings of Merck in the Advisory Action, stating that "Immediate Care" includes cognitive training procedures. Advisory Action, page 2. This is incorrect. Merck lacks any such teaching or suggestion, as just discussed. In addition, this statement is contrary to the medical references relating to stroke, incorporated in the instant application, which indicate that cognitive training is not provided until weeks — if not many months – after the acute phase of stroke has ended. *See* Supplemental Response, page 23. It also contradicts evidence previously submitted by the Applicant, such as the authoritative National Clinical Guidelines on Post-Stroke Rehabilitation, which teach that rehabilitation and cognitive training does not occur until the acute stroke phase has ended and the patient's medical condition has stabilized and fully assessed. *See* Supplemental Response, pages 22-23. Moreover, the Advisory Action *still* fails to explain how an alleged overlap between Merck and Christensen teaches or suggest administering PDE4 inhibitors in *conjunction* with cognitive training and then *repeating* this conjunction step one or more times, as explicitly required in the present claims.

Accordingly, it is respectfully asserted that the Examiner has not – and cannot – make a proper showing that the prior art teaches or suggests all elements of the claimed invention. The threshold for a prima facie case is therefore not met, and the rejection is clearly erroneous.

II. The Prior Art Does Not Provide Sufficient Motivation to Administer PDE4 Inhibitors in Conjunction with Cognitive Training.

The Examiner argues that "since both references teach treating stroke patients, it is obvious to combine these treatment regimens because both are drawn to the same purpose as well as for the combined therapeutic effect." OA at 9. This argument is an oversimplification that fails to recognize that stroke care comprises clinically and temporally distinct stages. June Reply, pages 18-19. With knowledge of these different stages, it is apparent that the prior art of record, if anything, would only one motivate one of

ordinary skill in the art to consider giving the claimed treatments *serially* to a stroke patient: administering PDE4 inhibitors at the onset of stroke during the acute phase; and after some time interval, providing cognitive training during the rehabilitation phase. June Reply, page 17.

Such serial treatment regimens are *not* the claimed invention. The Examiner's reference to the "same purpose" therefore improperly elevates semantics over substance. While PDE4 inhibitor administration and cognitive training may both serve the ultimate purpose of treating stroke, how and when they do so is completely different. The prior art shows that the purpose of PDE4 inhibitor administration is to treat *acute* stroke conditions triggered by TNF activation in medically unstable patients, whereas the purpose of cognitive training is to improve cognitive function in medically stable patients during *rehabilitation*. *See, e.g.,* June Reply, page 19. Again, this is not the claimed invention.

In sum, the Examiner has failed to establish a proper motivation for combining Christensen and Merck in a way that would meet the instant claims: There is no basis for administering PDE4 inhibitors *in conjunction* with cognitive training, so that CREB pathway function is enhanced during cognitive training, much less a basis for *repeating* this conjunction step one or more times – as required by the claims. Accordingly, it is respectfully asserted that the Examiner has not established a *prima facie* case for obviousness – and cannot do so.

CONCLUSION

In light of the foregoing, Applicant respectfully requests that the Panel withdraw the rejections of record and allow the claims as presently drafted, or alternatively, re-open prosecution on the merits. If the Panel has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this Brief Request for Review, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully Submitted,

/djpelto Reg. No. 33754/

August 27, 2010

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